Differential Electrophysiological Effects of β_1- vs β_2- Adrenergic Stimulation in the Isolated Canine Right Atrium

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Objective

To investigate the differential electrophysiological roles of β_1- vs β_2-adrenergic (AR) stimulation on regulating pacemaker activity in the isolated right atrium of a large mammalian model.

Introduction

Excessive β-AR stimulation is a hallmark of heart failure (HF) [1]. In the development of end-stage HF, cardiac output is reduced and myocardial function declines. The sympathetic nervous system compensates for these losses by activating β-AR receptors and thus increasing heart rate and cardiac contractility [2]. Specifically, circulating catecholamine levels rise to regulate G-protein-coupled receptor activity and hemodynamic demands. Acutely, β-AR receptor activation can effectively return cardiac conditions back to normal levels; however, chronic sympathetic activity may be deleterious to the heart and actually lead to further pathologic changes and deterioration of both cardiac structure and function [2].

There are two dominant subtypes of β-AR: $\beta_1$and β_2. The signaling and functional properties of these two adrenergic receptors are distinctly different (Fig. 1). β1-AR mediates chonotropic and inotropic effects of catecholamines via the stimulatory G protein (Gs), whereas β2-AR can to couple to both Gs and the inhibitory G protein (Gi) [2].

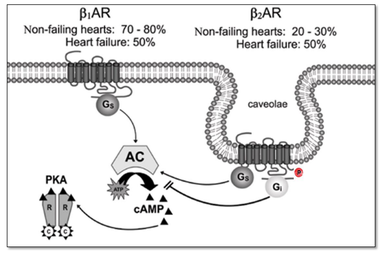


Figure 1. Intracellular signaling pathways and subcellular localization of β_1- and β_2- AR receptors in cardiomyocytes. β_1-AR mediates effects of catecholamines via Gs. β_2-AR can couple to Gs to mediate the contraction rate of cardiomyocytes, but it can also couple to Gi to have an antiapoptotic effect on cardiomyocytes [2].

Background & Motivation

β-blockers are a mainstay therapy for many of those who suffer from heart failure, but it is not fully understood how β-AR stimulation directly affects pacemaker activity. Recent studies have shown that stimulation of β_1- and β_2-AR has varying electrophysiological responses and arrhythmogenic effects on the heart, specifically in the ventricles (Fig. 2) [1]. Therefore, it was the goal of this study to examine the electrophysiological roles of β_1- vs β_2-AR stimulation on the right atrium of a large animal model to better understand their differential effects in regulating pacemaker activities.

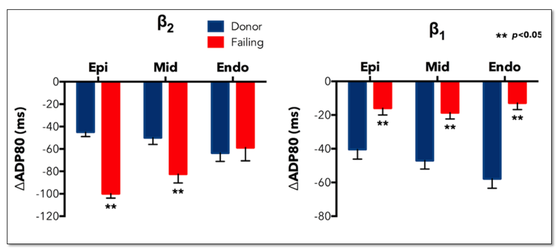
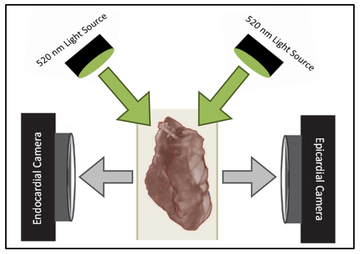


Figure 2. In human ventricular tissue, both β_1- and β_2-AR stimulation reduces action potential durations (APDs). In healthy donor hearts, β_2 reduces APD to a larger degree than does β_1. The opposite effect is observed in failing hearts, demonstrating that the β_2-AR pathway is sensitized in HF, whereas β_2 is desensitized [1].

Methods

Figure 3. Schematic representation of dual-sided optical mapping setup. Isolated canine right atrial preparation is placed in a temperature controlled bath at 37°C and perfused with oxygenated Tryode solution. The tissue is suspended vertically to allow optical access to both endocardial and the epicardial surfaces. Each side of the preparation is excited with a 520-nm LED light source, and emitted fluorescence captured through a 690-nm long-pass filter using two MICAM Ultima-L CMOS cameras facing eachother with the same 5×5 cm field of view. Recordings were captured at 1000 Hz.



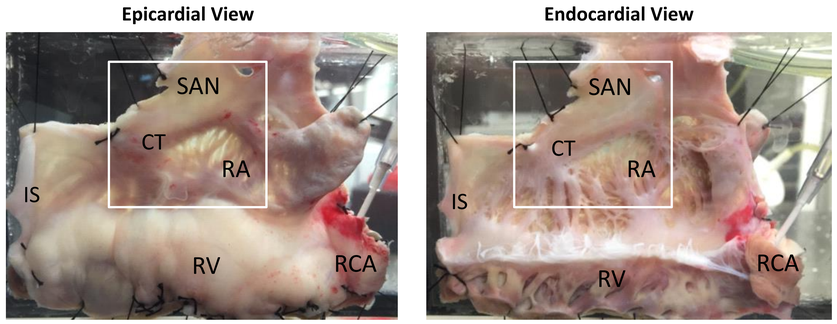


Figure 4. Representative views of epicardial (left) and epicardial (right) surfaces of the isolated canine right atrium. SAN indicates sinoatrial node; CT, crista terminalis; RA, right atrium; RV, right ventricle; IS, interatrial septum; RCA, right coronary artery (cannulated).

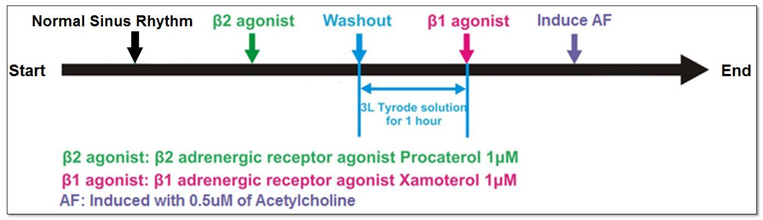


Figure 5. Detailed timeline of the experimental protocol. Specific agonists for β_2-AR and β_1-AR (procaterol at 1μmol/L and xamoterol at 1μmol/L, respectively) were perfused into the preparation. Agonists were applied at saturating concentrations according to previous cardiac studies [1] so that the maximum effective activation of the receptors could be achieved.

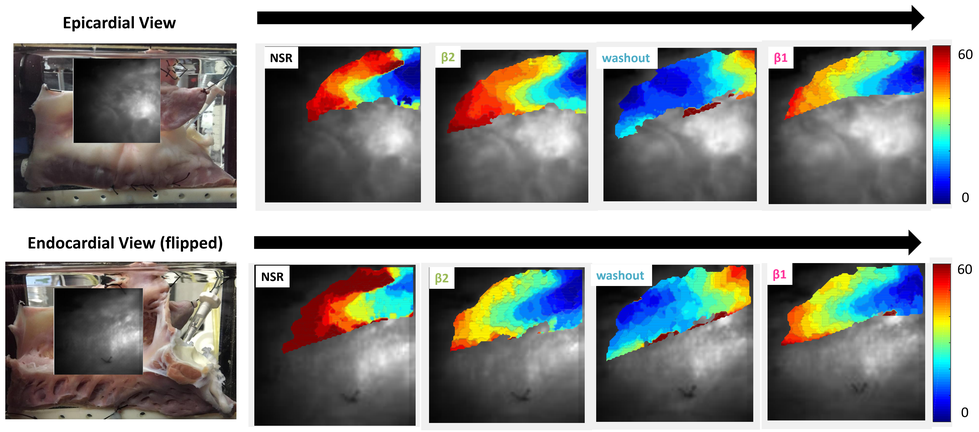


Figure 6. Representative activation maps of the isolated canine right atrium upon pharmacological stimulation of β_1- and β_2-AR.

Results

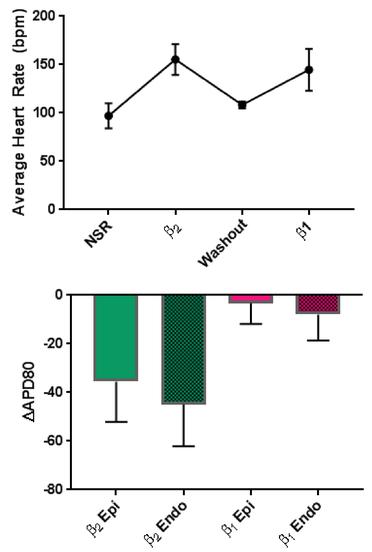


Figure 7. Changes in average heart rate and APD80 with sympathetic pharmacological stimulation.

Top: Average heart rate (HR) at each step of the protocol (n=3). Error bars represent standard deviation.

Bottom: Changes in Action Potential Duration at 80% (APD80) in the isolated RA, calculated as the difference of APD between baseline and in the presence of β-ARs (n=3). Error bars represent standard deviation.

Conclusions

- This data shows, for the first time, a differential electrophysiological role of β_1 and β_2 in right atrial tissue of a large animal model.
- Both β-ARs increase automaticity of pacemaker tissue, but β_2 has a larger impact than β_1 in decreasing APD80.
- Dual-sided optical mapping is beneficial for showing shifts in the leading pacemaker initiation sites in the presence of adrenergic agonists.
- In contrast to effects observed in normal ventricular tissue, β-ARs subtypes play opposing roles in regulating action potential duration in the right atrium.
- The results of this study offers new insights into the differential role of β_1 and β_2 in regulating heart rate and the propagation of electrical activity throughout pacemaking tissue.

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References

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